REMARKS

Amendments to the Claims

Claims 48, 50, 53-55, 57-60, 62, 69, 70, 73 and 75 are pending. The Applicants respectfully ask the Examiner to replace all prior versions and listings of claims in the present application with the listing of claims currently provided. Claims 48 and 50 were amended. The Applicants hereby state that all amendments do not add new subject matter to the specification.

Claim 48 and 50 amendment support directed towards a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42 can be found throughout the present specification, such as, *e.g.*, p. 19, line 28 though p. 20, line 6; and FIG. 8.

Summary of April 10, 2008 Interview Pursuant to 37 C.F.R. § 1.133(b)

The Applicants wish to thank Examiner Archie and Examiner Navarro for the telephone interview on April 10, 2008. Pending Claims 48 and 50 were discussed in view of the outstanding December 12, 2007 Office Action rejection alleging a lack written description pursuant 35 U.S.C. § 112, ¶ 1, novelty pursuant 35 U.S.C. § 102(b), and unobviousness pursuant 35 U.S.C. § 103. The parties agreed that, barring the identification of any new prior art, the amendments and replies set forth below would result in allowable subject matter.

Rejection Pursuant to 35 U.S.C. § 112, ¶ 1 Written Description

The Examiner has rejected Claims 48, 50, 53-55, 57-60, 62, 69, 70, 73, and 75 as allegedly failing to comply with the written description requirement under 35 U.S.C. § 112, ¶ 1. Specifically, the Examiner contends that the specification fails to teach any structural limitations of SNAP-25. The Applicants respectfully ask for reconsideration pursuant to 37 C.F.R. § 1.111.

Currently amended Claims 48 and 50 are now directed, in part, toward a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42. Therefore, the Applicants submit that the present specification provides adequate written description support for all claims and respectfully request withdrawal of the 35 U.S.C. § 112, ¶ 1 written description rejection against Claims 48, 50, 53-55, 57-60, 62, 69, 70, 73, and 75.

Rejection Pursuant to 35 U.S.C. § 102(b) Anticipation

The Examiner has rejected Claims 48, 50, 53-55, 57-60, and 62 as allegedly being anticipated under 35 U.S.C. § 102(b) by Mauricio Montal, *Peptide inhibitors of Neurotransmitter Secretion by Neuronal Cells*, International Patent Publication WO 97/34620 (Feb. 4, 1997), hereafter the "Montal publication." The Examiner contends that the Montel publication teaches a SNAP-25 variant having at least 95.4% identity to SEQ ID NO: 42. December 12, 2007 Office Action at p. 7, ¶ 4, lines 4-5. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

According to *MPEP* § 2131, for a reference to anticipated a pending claim, that reference must teach each and every element of the pending claim.

I. The Montal publication discloses a different method.

Presently amended Claims 48 and 50 are directed, in part, towards a method of treating or preventing poisoning by a clostridial toxin in a patient by administering a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25. The administered SNAP-25 polypeptides are resistant to proteolytic cleavage by the Clostridial toxin and are capable of performing the function of the target protein and/or are capable of inhibiting the proteolytic activity of the toxin. Present specification at p. 4, line 24-28. The SNAP-25 polypeptides rescue the exocytotic function in clostridial toxin-poisoned cells, thereby restoring the ability of a neuron to secret neurotransmitters, and as such, are useful as a treatment of clostridial toxin poisoning, such as, *e.g.*, botulism. *Id.* As such, the presently claimed method is directed

toward treating or preventing Clostridial toxin poisoning by administering a SNAP-25 polypeptide that rescues neuronal cells from the poisoning by restoring neurotransmitter secretion.

The Montal publication discloses a method of inhibiting secretion of neurotransmitters from synaptic vesicles by administering Excitation-Secretion Uncoupling Peptides (ESUPs) that mimic Clostridium neurotoxins by inhibiting secretion of neurotransmitters from neuronal vesicles into the neuromuscular junction. *See e.g.*, Montal publication at p. 2, lines 6-12. As such, the Montal publication discloses a method of inhibiting neurotransmitter secretion by administering a peptide that mimics Clostridial neurotoxin paralysis.

Thus, the Applicants respectfully submit that the Montal publication does not anticipant the presently claimed method because this publication teaches a method of inhibiting neurotransmitter secretion by administering a peptide that mimics Clostridial neurotoxin paralysis. As such, the Montal publication does not read on a method of treating Clostridial neurotoxin poisoning. Therefore, the Applicants respectfully submit that this rejection is unsupported and request withdrawal of the 35 U.S.C. § 102(b) anticipation rejection for Claims 48, 50, 53-55, 57-62, 69 and 70.

II. The Montal publication discloses different peptides.

Presently amended Claims 48 and 50 are directed, in part, towards a toxin-resistant SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42 that is capable of supporting Ca^{2+}-mediated exocytosis, but resistant to proteolysis by the clostridial toxin or a toxin-inhibitory SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42 that is capable of supporting Ca^{2+}-mediated exocytosis, but further capable of inhibiting the protease activity of the clostridial toxin. The present specification discloses that SEQ ID NO: 42 is the 206 amino acid sequence of full-length SNAP-25. Present specification, Sequence Listing, SEQ ID NO: 42.

The Montal publication consists of peptides called ESUPs that correspond in sequence to all or a portion of the substrate binding domain of 1) VAMP for SNAP-25 and Syntaxin; 2)

SNAP-25 for VAMP and Syntaxin; pr 3) Syntaxin for VAMP and SNAP-25. Montal publication at p. 3, lines 11-14; p. 10, lines 10-13; FIGS. 3-5. This publication indicates that for optimal activity, ESUPs have a minimum length of about 20 amino acids and a maximal length of about 28 amino acids. *Id.* at p. 3, lines 8-9. This Montal publication discloses eight SNAP-25 ESUPs ranging from 7 to 26 amino acids in length, each derived from the SNAP-25 substrate binding domain which corresponds to amino acids 167-206 of full-length SNAP-25. *Id.* at p. 8, lines 14-20; FIG. 3; SEQ ID NO: 7-SEQ ID NO: 13. These fragments are incapable of supporting Ca^{2+}-mediated exocytosis. In addition, because each fragment contains a wild-type sessile bond (*i.e.* R_{180}–I_{181} or Q_{197}–R_{198}; FIG. 3) each peptide is susceptible to proteolytic cleavage by a clostridial toxin.

Thus, the Applicants respectfully submit that the Montal publication does not anticipant the presently claimed method because this publication discloses SNAP-25 peptide fragments of between 6-28 amino acids in length that inhibit neurotransmitter release and cannot support Ca^{2+}-mediated exocytosis. Furthermore, these SNAP-25 peptide fragments are not resistant to proteolysis by the clostridial toxin. As such, the Montal publication does not read on a toxin-resistant SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42 that is capable of supporting Ca^{2+}-mediated exocytosis, but resistant to proteolysis by the clostridial toxin or a toxin-inhibitory SNAP-25 that is a SNAP-25b variant having at least 95% identity to SEQ ID NO: 42 that is capable of supporting Ca^{2+}-mediated exocytosis, but further capable of inhibiting the protease activity of the clostridial toxin. Therefore, the Applicants respectfully submit that this rejection is unsupported and request withdrawal of the 35 U.S.C. § 102(b) anticipation rejection for Claims 48, 50, 53-55, 57-62, 69 and 70.

Rejection Pursuant to 35 U.S.C. § 103(a) Obviousness

I. Montal.

The Examiner has rejected Claims 48, 50, 69, and 70 as allegedly being obvious under 35 U.S.C. § 103(a) by the Montal publication. The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

A. Montal teaches away from claimed methods.

According to *MPEP* § 2143, to render a pending claim obvious, a reference must expressly or impliedly teach or suggest the claimed subject matter. If a prior art reference teaches away from the presently claimed invention, then a *prima facie* case of obviousness cannot be maintained. See *MPEP* §§ 2141.02; 2145.

As discussed above, the presently claimed methods are directed, in part, towards treating or preventing poisoning by a Clostridial toxin in a patient by administering a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25. This result is achieved by the fact that these administered SNAP-25 molecules rescue the exocytotic capability of the poisoned neuronal cells, thereby restoring the ability of neuronal cells to release neurotransmitters.

The Examiner indicates that the Montal publication teaches "a method of inhibiting the release of neurotransmitters from neuronal cells in a host comprising administering a therapeutically effective dosage of the agent (SNAP-25) into neuronal cells of a host in lieu of a Clostridial neurotoxin to provide a therapeutic benefit to the host. " December 12, 2007 Office Action at p. 9, ¶ 2, lines 2-6.

Thus, The Applicants respectfully submit that the Montal publication teaches away from the presently claimed methods because 1) it discloses a method of inhibiting neurotransmitter release, instead of teaching a method of restoring neurotransmitter release; and 2) its disclosed SNAP-25 peptides mimic Clostridial toxins by poisoning neuronal cells, instead of teaching SNAP-25 molecules that rescue neuronal cell from poisoning.

B. Proposed modification renders Montal unsatisfactory for its intended purpose

According to *MPEP* § 2143.01, "[i]f proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification."

The Applicants respectfully submit that the SNAP-25 peptides disclosed in the Montal publication function by inhibiting neurotransmitter release. The presently claimed toxin-resistant SNAP-25 or toxin-inhibitory SNAP-25 molecules function by restoring neurotransmitter release. Thus, modifying the Montal publication SNAP-25 peptides to function as a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 molecule would make these peptide unsatisfactory for its intended use because the Montal publication SNAP-25 peptides would no longer be able to inhibit neurotransmitter release.

C. Proposed modification changes principle of operation of Montal.

According to *MPEP* § 2143.01, "[i]f the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious."

As discussed above, the Montal publication SNAP25 peptides inhibit neurotransmitter release, whereas the presently claimed SNAP-25 molecule restore neurotransmitter release. As such, modifying the Montal publication SNAP-25 peptides to function as a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 molecule would change the principle of operation of these peptides because the Montal publication SNAP-25 peptides would no longer operate by inhibiting neurotransmitter release.

D. Conclusion.

Thus, the Applicants respectfully submit that a *prima facie* obviousness case cannot be made because the method of inhibiting neurotransmitter release taught by the Montal publication 1) teaches away from the presently claimed methods. In addition, modifying the method disclosed in the Montal publication, as suggested by the Examiner, would render the disclosed peptides and methods unsatisfactory for their intended purpose and change the principle of operation of these peptides and methods. Therefore, the Applicants respectfully submit that the Examiner's rejection is unsupported by the art and respectfully request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 48, 50, 69, and 70.

II. Montal and Schimidt.

The Examiner has rejected Claims 48, 50, 73, and 75 as allegedly being obvious under 35 U.S.C. § 103(a) by the Montal publication in view of James J. Schmidt et al. *Type A Botulinum Neurotoxin Proteolytic Activity: Development of Competitive Inhibitors and Implications for Substrate Specificity at the S_1' Binding Site*, 435 FEBS Lett. 61-64, hereafter the "Schmidt reference." The Applicants respectfully ask for reconsideration under 37 C.F.R. § 1.111.

As discussed above, the Montal publication teaches away from the presently claimed methods; and modifying the peptides and methods disclosed in the Montal publication, as suggested by the Examiner, would render these peptides and methods unsatisfactory for their intended purpose and change the principle of operation of these peptides and methods.

The Examiner cites the Schmidt reference for teaching N-acetyl-CRATKML-carboxamide, an inhibitor of clostridial toxin. As such, the Schmidt reference is completely silent with respect to any method of preventing or treating poisoning by a clostridial toxin, let alone any method of of preventing or treating poisoning by a clostridial toxin by administering a toxin-resistant SNAP-25 or a toxin-inhibitory SNAP-25 as presently claimed. As such, the Schmidt reference cannot make of for any of the deficiencies present in the Montal publication.

Thus, a *prima facie* obviousness case cannot be made because the method of inhibiting neurotransmitter release taught by the Montal publication 1) teach away from the presently claimed methods. In addition, modifying the method disclosed in the Montal publication, as suggested by the Examiner, would render the disclosed peptides and methods unsatisfactory for its intended purpose and change the principle of operation of these peptides and method. Furthermore, the Schmidt reference fails to teach any relevant aspect of the presently claimed methods or compensate for the deficiencies of the Montal publication. As such, the combined teachings of the Montal publication and the Schmidt reference do not render the presently claimed methods obvious. Therefore, the Applicants respectfully submit that the Examiner's rejection is unsupported by the art and respectfully

request withdrawal of the 35 U.S.C. §103(a) obviousness rejection for Claims 48, 50, 73, and 75.

CONCLUSION

For the above reasons the Applicants respectfully submit that the claims are in condition for allowance, and the Applicants respectfully urge the Examiner to issue a Notice to that effect. The Examiner is invited to call the undersigned agent if there are any questions. Please use Deposit Account 01-0885 for the payment of any extension of time fees under 37 C.F.R. § 1.136 or any other fees due in connection with the current response.

Respectfully submitted,

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